Enhanced Striatal Dopamine Release to Expectation of Alcohol: A Potential Risk Factor for Alcohol Use Disorder

Supplemental Information

Participants

Recruitment Procedures

Recruitment and study procedures began in 2012 at Yale for 6 participants (4 FHN and 2 FHP) pending availability of the radioligand [^{11}C]raclopride at Columbia, followed in 2013-2015 by an additional 49 participants at the Division of Translational Imaging at the New York State Psychiatric Institute/Columbia University. Recruitment was through newspaper, internet, and flyer advertisements. Participants were matched on age and sex across groups (FHN, FHP, AUD) and across subgroups counterbalanced for drink order (alcohol followed by placebo, AP; placebo followed by alcohol, PA). Data for the remaining 10 of the 65 participants (5 FHP and 5 FHN) were previously published (1). Criteria for selecting participants from the prior study (1) were purely demographic (sex, family history status, age, and drink order), and the lack of balance across these criteria in Ref. (1) limited the number of participants we could select for inclusion in the current study.

Inclusion and Exclusion Criteria

All participants were medically healthy by history, physical examination, EKG, and laboratory tests of blood and urine including urine toxicology screen testing for benzodiazepines, cannabinoids, phencyclidine, amphetamines, barbiturates, cocaine,

methadone, and opiates. Participants were excluded for recent or current use of psychotropic medications, more than one risk factor for coronary artery disease, systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg at screening or on day of alcohol administration, or for pregnancy or lactation or failure to use a reliable birth control method. Participants were free of any psychotic illness and AUD participants were free of obsessive-compulsive disorder, posttraumatic stress disorder, panic disorder, or history of severe alcohol withdrawal symptoms including seizures, delirium tremens, or symptoms likely to interfere with study procedures such as agitation, tremor, or sensory disturbances.

Monitoring and Safety Procedures

All FHN and FHP subjects participated on an outpatient basis, as did AUD participants who were free of history of significant withdrawal symptoms. AUD participants who presented a risk of withdrawal symptoms were admitted to an inpatient unit on the day prior to each PET scan and until the day following the scan, where they were monitored with vital signs every four hours and with the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) (2) by a study physician or research staff 3 times daily. Hospitalized participants were prescribed oral thiamine 100 mg per day, folate 1mg per day, and a multivitamin tablet daily. Lorazepam 1 mg every 4 hours was available as needed for significant withdrawal signs or symptoms noted clinically or as indicated by blood pressure over 150/100 mm Hg; or increase of 20 mm Hg over baseline; or pulse increase of 20/min over baseline; or CIWA-Ar rating above 8. None of the 15 AUD

participants exhibited significant withdrawal symptoms during hospitalization or scanning procedures and none received lorazepam.

Table S1. Participant Demographics by Drink Order, n = 63 completers

Demographic variable	FHP		FHN		AUD	
Drink Order	AP	PA	AP	PA	AP	PA
n	8	8	15	17	8	7
Age* (years ± standard deviation)	24.7 ± 2.6	26.1 ± 2.7	28.7 ± 6.4	29.7 ± 8.2	36.6 ± 10.0	35.8 ± 10.4
Sex (F, M)	4, 4	4, 4	7, 8	8, 9	4, 4	4, 3

AP, Alcohol beverage first PET scan; PA, Alcohol beverage second PET scan

* Mean ± standard deviation

Table S2. [^{11}C]Raclopride scan characteristics *

PET parameters	Placebo Scan	Alcohol Scan	p
ID, mCi	11.8 ± 3.2	11.6 ± 3.4	.65
IM, μgm	2.2 ± 1.5	1.9 ± 1.2	.32

ID; injected dose of [^{11}C]raclopride; IM, injected mass of [^{11}C]raclopride

* Mean ± standard deviation

Table S3. Ventral striatal ΔBP_{ND} by group and drink order

Group	FHP		FHN		AUD	
Drink Order	AP	PA	AP	PA	AP	PA
n	8	8	15	17	8	7
VST ΔBP_{ND} (%)*	11.7 ± 1.4	2.7 ± 1.9	5.3 ± 2.4	7.5 ± 1.6	4.0 ± 2.5	7.3 ± 1.6

AP, Alcohol beverage first PET scan; PA, Alcohol beverage second PET scan.

* Mean ± standard error of the mean

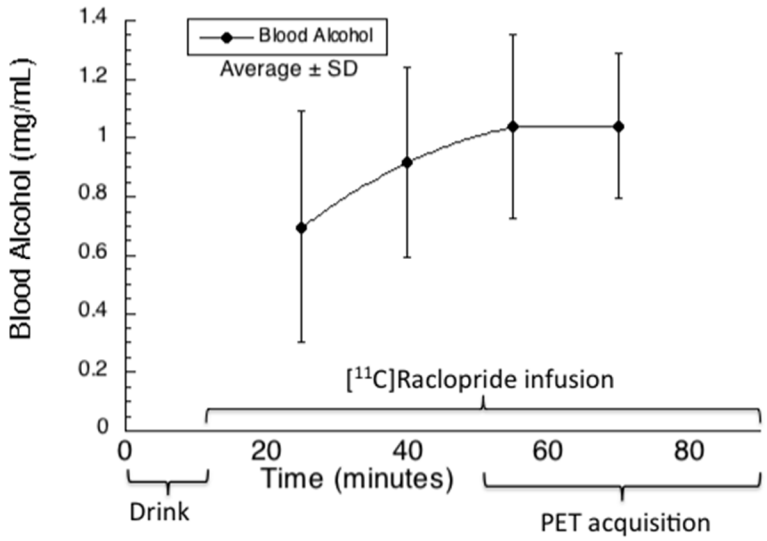

Figure S1. Blood alcohol levels and PET scan timeline

Blood samples drawn at 25, 40, 55, and 75 min following the beginning of the alcohol beverage consumption were assayed for alcohol levels which are shown in relation to [^{11}C]raclopride infusion and PET scan timing. Depicted are means and standard deviations of the assay values. Blood levels were available for n = 55 of the 63 participants who consumed the alcohol beverage.

Baseline BP_{ND}

Here, we describe the relationship between the ΔBP_{ND} we report in this paper and the hypothetical ΔBP_{ND} that would have been observed had BP_{ND} under each of the conditions, placebo and alcohol, been tested relative to a baseline value. We assume that the baseline is stable, i.e. the baseline value was the same on both days.

Let BP_{ND}(condition) = BP_{ND} during the condition, where condition takes on the values baseline, placebo or alcohol.

Let ΔBP_{ND}(condition 1, condition 2) be the difference between conditions 1 and 2 relative to condition 1,

$$\Delta BP_{ND}(\text{condition 1,condition 2}) = 1 - \frac{BP_{ND}(\text{condition 2})}{BP_{ND}(\text{condition 1})}$$

where, for mathematical convenience, ΔBP_{ND} is expressed such that a decrease in BP_{ND} under condition 2 compared to condition 1 will have a positive sign. Then the relationship between ΔBP_{ND}(placebo, alcohol), ΔBP_{ND}(baseline, alcohol) and ΔBP_{ND}(baseline, placebo) is as follows

$$\Delta BP_{ND}(\text{baseline,alcohol}) - \Delta BP_{ND}(\text{baseline,placebo}) =$$
$$\left(1 - \frac{BP_{ND}(\text{alcohol})}{BP_{ND}(\text{baseline})}\right) - \left(1 - \frac{BP_{ND}(\text{placebo})}{BP_{ND}(\text{baseline})}\right) =$$
$$\frac{BP_{ND}(\text{placebo}) - BP_{ND}(\text{alcohol})}{BP_{ND}(\text{baseline})} =$$
$$\Delta BP_{ND}(\text{placebo,alcohol}) \times \frac{BP_{ND}(\text{placebo})}{BP_{ND}(\text{baseline})}$$

That is, the observed percent difference in BP_{ND} between the placebo and alcohol conditions will be the difference between the percent differences of each of these relative to baseline, amplified by the factor BP_{ND}(baseline)/BP_{ND}(placebo). Two qualitative

observations can be made about this relationship. First, the direction of change is preserved, i.e. the assumption that baseline is unchanged across days means that if ΔBP_{ND}(placebo, alcohol) > 0 then ΔBP_{ND}(baseline, alcohol) > ΔBP_{ND}(baseline, placebo). The second is, assuming there is an effect during the placebo condition, i.e. BP_{ND}(baseline) > BP_{ND}(placebo), then the reported ΔBP_{ND} in this study, ΔBP_{ND}(placebo, alcohol) will be increased in magnitude compared to the difference across conditions. In particular, the negligible difference across conditions observed in the FHP-PA group would have been even smaller, had it been expressed relative to baseline.

Supplemental References

1. Urban NB, Kegeles LS, Slifstein M, Xu X, Martinez D, Sakr E, et al. (2010): Sex differences in striatal dopamine release in young adults after oral alcohol challenge: a positron emission tomography imaging study with [11C]raclopride. *Biological psychiatry*. 68:689-696.
2. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM (1989): Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *British journal of addiction*. 84:1353-1357.